Ticagrelor to Reduce Myocardial Injury in Patients With High-Risk Coronary Artery Plaque

ORIGINAL RESEARCH

Ticagrelor to reduce myocardial injury in patients with high-risk coronary artery plaque

Alastair J. Moss MD[1], Marc R. Dweck MD PhD[1], Mhairi K. Doris MD[1], Jack P. M. Andrews MD[1], Rong Bing MD[1], Rachael O. Forsythe MD PhD[1], Timothy R. Cartlidge MD[1], Tania A. Pawade MD PhD[1], Marwa Daghem MD[1], Jennifer B. Raftis PhD[2], Michelle C. Williams MD[1,3], Edwin J. R. van Beek MD PhD[1,3], Laura Forsyth PhD[4], Steff C. Lewis PhD[4], Robert Lee[4], Anoop S.V. Shah MD PhD[1,5], Nicholas L. Mills MD PhD[1,5], David E. Newby MD PhD[1,3], Philip D. Adamson MD PhD[1, 6]

[1]British Heart Foundation Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK
[2]Medical Research Council Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK
[3]Edinburgh Imaging, Queen's Medical Research Institute University of Edinburgh, Edinburgh, UK
[4]Edinburgh Clinical Trials Unit, University of Edinburgh, Edinburgh, UK
[5]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK
[6]Christchurch Heart Institute, University of Otago, Christchurch, New Zealand

Correspondence to:
Dr Alastair J Moss
BHF Centre for Cardiovascular Science
Chancellor's Building
University of Edinburgh
49 Little France Crescent
Edinburgh
EH16 4SB
UNITED KINGDOM
Email: amoss@staffmail.ed.ac.uk

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Structured Abstract

Background

High-risk coronary atherosclerotic plaque is associated with higher plasma troponin concentrations suggesting ongoing myocardial injury that may be a target for dual antiplatelet therapy.

Objectives

To determine whether ticagrelor reduces high-sensitivity troponin I concentrations in patients with established coronary artery disease and high-risk coronary plaque.

Methods

In a randomized double-blind placebo-controlled trial, patients with multivessel coronary artery disease underwent coronary 18F-fluoride positron emission tomography-computed tomography and measurement of high-sensitivity cardiac troponin I and were randomized (1:1) to ticagrelor 90 mg twice daily or matched placebo. The primary endpoint was troponin I concentration at 30 days in patients with increased coronary 18F-fluoride uptake.

Results

In total, 202 patients were randomized and 191 met the pre-specified criteria for inclusion in the primary analysis. In patients with increased coronary 18F-fluoride uptake (n=120/191) there was no evidence that ticagrelor had an effect on plasma troponin concentrations at 30 days (ratio of geometric means for ticagrelor *versus* placebo, 1.11, [95% confidence interval 0.90 to 1.36], p=0.32). Over 1 year, ticagrelor had no effect on troponin concentrations in patients with increased coronary 18F-fluoride uptake (ratio of geometric means, 0.86, 95% confidence interval 0.63 to 1.17, p=0.33).

Conclusions

Dual antiplatelet therapy with ticagrelor does not reduce plasma troponin concentrations in patients with high-risk coronary plaque, suggesting that subclinical plaque thrombosis does not contribute to ongoing myocardial injury in this setting.

Clinical Trials.gov Study ID: NCT02110303

Keywords

Myocardial infarction, Troponin, 18F-fluoride

Condensed Abstract

In a double-blind randomized placebo-controlled trial, 191 patients with multivessel coronary artery disease underwent 18F-fluoride positron emission tomography and computed tomography coronary angiography. In patients with high-risk plaque defined by 18F-fluoride uptake in at least one coronary plaque (n=120/191), there was no evidence that dual antiplatelet therapy with ticagrelor affected 30-day plasma troponin concentrations (ratio of geometric means 1.11 [95% confidence interval 0.90-1.36], p=0.32). This suggests that subclinical plaque thrombosis does not contribute to ongoing myocardial injury in patients with multivessel coronary artery disease and higher risk plaque.

List of Abbreviations

ECG – Electrocardiogram

MBq - Megabecquerel

PET-CCTA – Positron emission tomography – Coronary computed tomography angiography

PLATO – PLATelet inhibition and patients Outcomes Trial

SUV_{MAX} – maximum standardized uptake value

TBR – Tissue to background ratio

Introduction

Coronary plaque rupture is the commonest cause of acute coronary thrombosis and myocardial infarction (1). Patients who have an increased risk of recurrent plaque rupture events may benefit from intensification of secondary prevention therapy (2). In this regard, the addition of a $P2Y_{12}$ receptor antagonist to low-dose aspirin reduces the risk of cardiovascular death, myocardial infarction and stroke in patients with recent (3) or prior (4) myocardial infarction. Ticagrelor is an oral reversible antagonist of the platelet adenosine diphosphate $P2Y_{12}$ receptor. It provides faster, more potent and more consistent $P2Y_{12}$ inhibition than clopidogrel (5). In the PLATelet inhibition and patients Outcomes (PLATO) trial of 18,624 patients presenting with acute coronary syndrome, ticagrelor was superior to clopidogrel for the prevention of cardiovascular events and death (3). Moreover, the prolonged use of dual antiplatelet therapy following myocardial infarction continues to reduce cardiovascular events, albeit at the expense of increased rates of major bleeding (4). Thus, there is a clinical need to improve the risk stratification of patients to enable physicians to better select 'vulnerable' patients who may benefit from extended duration of dual antiplatelet therapy.

A novel approach for assessing patients at high-risk of coronary plaque rupture is using positron emission tomography and coronary computed tomography angiography (PET-CCTA). This technique uses the radiotracer 18F-fluoride to identify regions of increased disease activity in coronary artery plaques. Previous studies have demonstrated that coronary 18F-fluoride uptake correlates with a high-risk cardiovascular profile and identifies ruptured coronary plaques in patients with recent myocardial infarction (6, 7). Importantly, we have previously reported an association between increased coronary 18F-fluoride uptake and higher plasma high-sensitivity cardiac troponin I concentrations in patients with stable

coronary artery disease (7). Silent plaque rupture is common and subclinical plaque thrombus formation is a frequent incidental post-mortem finding in patients with multivessel coronary artery disease who have died from non-cardiovascular causes (8). This suggests that coronary 18F-fluoride uptake may identify high-risk plaque that is associated with thrombus formation and subclinical myocardial injury from microemboli. If correct, this would potentially be modifiable with intensive dual antiplatelet therapy.

In this study, we assessed whether coronary 18F-fluoride activity identifies patients with stable multivessel coronary artery disease who respond favorably to ticagrelor as assessed by a reduction in high-sensitivity cardiac troponin I concentrations.

Methods

Study Design

This was an investigator-initiated double-blind randomized parallel-group placebo-controlled trial conducted at a single centre in Edinburgh, UK. The study was approved by the local institutional review board, the Scottish Research Ethics Committee (REC reference: 14/SS/0089), Medicines and Healthcare products Regulatory Agency, and the United Kingdom (UK) Administration of Radiation Substances Advisory Committee. It was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent prior to any study procedures.

Study Population

Patients were recruited between March 2015 and March 2017. Patients were included if they met the following criteria: age ≥40 years and already receiving aspirin therapy with angiographically proven multivessel coronary artery disease defined as at least two major epicardial vessels with any combination of either (a) >50% luminal stenosis, or (b) previous revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). Patients were excluded if they had any of the following criteria: an acute coronary syndrome within the last 12 months, any ongoing indication for dual anti-platelet therapy, or concurrent thienopyridine (clopidogrel or prasugrel) or oral anticoagulant therapy, or percutaneous coronary intervention or coronary artery bypass graft surgery within the last 3 months. Full eligibility criteria are provided in the ***Supplementary Table 1***.

Trial Intervention and Randomization

Patients were randomly assigned 1:1 to either ticagrelor 90 mg twice daily or matched placebo tablets (AstraZeneca, UK). Randomization was performed using a web-based system that ensured allocation concealment, with treatment allocation incorporating minimization based on age (<65, ≥65 years old), sex, baseline plasma high-sensitivity troponin I concentration (≤5.1, >5.1 ng/L) and the presence or absence of coronary 18F-fluoride uptake. A random element was included with a 1 in 10 chance of the determined treatment allocation being switched to the other treatment arm.

Study Procedures

All patients underwent a baseline assessment to confirm eligibility and measurement of plasma high-sensitivity cardiac troponin I concentration and platelet-monocyte aggregates. An electrocardiogram (ECG) gated 18F-fluoride PET-CTCA was performed after patients had received 50-100 mg of oral metoprolol if their resting heart rate was >65 beats/min prior to the intravenous administration of 250 MBq 18F-fluoride. After 60 min, patients were imaged with a hybrid PET-CT scanner (64-multidetector Biograph mCT, Siemens Medical Systems, Erlangen, Germany). Attenuation correction CT scans were performed prior to the acquisition of ECG-gated list-mode PET data using a single 30-min bed position centred on the heart. Finally, an ECG-gated CCTA was performed in mid-diastole during held expiration following sublingual glyceryl trinitrate.

Image Analysis

Positron emission tomography images were reconstructed in diastole (50-75% of the R-R interval, 2 iterations, 21 subsets Siemens Ultra-HD algorithm) and fused with contrast enhanced CCTA. Analysis of the CT images was performed using dedicated software (Vitrea

Advanced, Toshiba Systems) with multi-planar reformatting for plaque analysis as required. Coronary arteries with a diameter ≥2 mm were assessed according to the 18-segment Society of Cardiac Computed Tomography model. Qualitative and semi-quantitative analysis of the PET images was performed by trained observers using an OsiriX workstation (OsiriX version 3.5.1 64-bit; OsiriX Imaging Software, Geneva, Switzerland). The analysis of coronary 18F-fluoride activity has been described previously (6, 7). In brief, visual assessment for increased coronary 18F-fluoride activity was performed on both a per-patient level and per-segment basis. For a signal to be co-localised to the coronary artery, an atherosclerotic plaque had to be present on the CCTA and the increased pattern of radiotracer had to arise from the coronary artery and follow its course over >5 mm in three dimensions on orthogonal views. Semi-quantitative PET analysis was undertaken for all proximal coronary segments in addition to any atherosclerotic segment with focal 18F-fluoride activity as described above. Maximum standardized uptake values (SUV_{MAX}) were measured within regions of interest. Correction was made for uptake in a referent proximal coronary plaque with no evidence of increased 18F-fluoride activity. To calculate coronary target to background ratios (TBR), coronary SUV_{MAX} was divided by these background measures providing TBR_{MAX}. Coronary 18F-fluoride activity with TBR_{MAX} >1.25 was classified a high-risk plaque.

High-sensitivity cardiac troponin I

Plasma high-sensitivity cardiac troponin I concentrations were measured using the ARCHITECT*STAT* assay (Abbott Laboratories, Abbott Park, Illinois). The limit of detection is 1.0 ng/L with an inter-assay co-efficient of variation <10% at 4.7 ng/L (9). The upper reference limit (99^{th} centile) based on 4,590 samples from healthy men and women is 34 ng/L for men and 16 ng/L for women (10). Samples were collected at baseline, 30 days and 3, 6, 9

and 12 months. A value of 0.5 ng/L was imputed for troponin values below the limit of detection.

Platelet function analysis

Platelet and monocyte activation in response to adenosine diphosphate (ADP) was determined by flow cytometry, as described previously (11). These analyses were performed by a single technician blinded to study allocation with the results of these investigations withheld from the study team until after trial database lock. Briefly, peripheral venous blood was obtained from all participants at the baseline and 1-month visits. Blood was drawn by clean venepuncture of a large antecubital vein using a 19-gauge needle, and care was taken to ensure a smooth blood draw without venous stasis. Blood was collected into tubes containing the direct thrombin inhibitor, D-Phenylalanine-L-prolyl-L-arginine chloromethyl ketone (PPACK, Cambridge Biosciences). Tubes were gently inverted to ensure mixing of whole blood with anticoagulant.

Immunolabelling and flow cytometry were performed in whole blood to avoid centrifugation and washing steps which can lead to artefactual platelet activation. All chemicals were obtained from BD Biosciences. (Oxford, UK). Aliquots of whole blood (50 μL) were incubated with anti-CD14-Allophycocyanin (APC), anti-CD42a-fluorescein isothiocyanate (FITC), anti-CD11b-PE-Cyanine(Cy)7, anti-CD62p-Phycoerythrin (PE) and isotype matched controls for 20 min at room temperature in Eppendorfs with and without ADP (at final concentration of 20 μmol/L). Thereafter, samples were fixed with 1% paraformaldehyde (p-selectin) or FACS-Lyse (platelet-monocyte aggregates). All samples were analysed within 24 hours using a FACSCalibur flow cytometer (Becton-Dickinson). Data analysis was performed using FlowJo v10 (Treestar, Oregon, USA). A medium flow setting was used to

minimize leukocyte-platelet coincident events. Monocytes were identified based on their forward and side scatter characteristics and then by triggering on FL-4 to identify CD14-PE positive monocytes and exclude large granular lymphocytes. For each measurement a minimum of 2,500 monocytes were collected. Platelet-monocyte aggregates were defined as monocytes positive for CD42a. All results are expressed as geometric mean of fluorescence. P-selectin expression was defined as CD42a-FITC positive platelets that were also positive for CD62p-PE.

Study Endpoints

The pre-specified primary endpoint was high-sensitivity cardiac troponin I concentrations at 30 days in patients with increased coronary 18F-fluoride activity. Secondary endpoints were plasma high-sensitivity cardiac troponin I concentration at 30 days in patients without coronary 18F-fluoride activity, and plasma high-sensitivity troponin I concentration over 1 year. Adverse events were recorded in all patients who received a single dose of study medication and included bleeding events categorized according to PLATO criteria as major life-threatening, other major, minor or minimal bleeding (3).

Sample Size

In patients with increased coronary 18F-fluoride uptake, we previously reported that mean troponin concentrations were more than double those in patients without increased coronary 18F-fluoride uptake (7.9 [SD 9.3] vs. 3.1 [SD 1.9] ng/L, p=0.047) (7). It was estimated that ticagrelor would reduce troponin concentration by half. Forty-eight patients per treatment arm were required to achieve 80% power at two-sided $p<0.05$. After allowing for 15% drop-out, we estimated that fifty-five patients will be required per treatment arm. Previous studies had found that 45% of patients with advanced but stable coronary artery disease

demonstrated increased coronary 18F-fluoride uptake, so a total sample size of 250 patients was estimated to be required to identify 110 patients with increased coronary 18F-fluoride activity. Termination of further recruitment could be authorized by the trial steering committee once a per-protocol population of 110 patients with increased coronary 18F-fluoride activity had been randomized and completed the primary endpoint at 30 days.

Statistical Analysis

Categorical data are presented using counts and percentages, whilst continuous variables are presented using mean, standard deviation (SD), median, interquartile range, minimum, maximum, and number of patients. Participants were removed from formal statistical analysis where data were missing for that outcome variable. All (except safety) analyses were performed on a per-protocol population that excluded participants without a blood sample, or whose compliance was <80% for the study medication, at the 30-day visit. For the primary analysis, the change in troponin I concentration from baseline to 30 days was compared between the two treatment groups (ticagrelor and placebo) using linear regression, adjusting for the minimisation variables in patients with increased coronary 18F-fluoride uptake. Prior to analysis, tests for normality were undertaken and, where data were skewed, logarithmic transformation was performed. Central estimates and 95% confidence intervals (CI) were calculated. Similar analyses were performed for secondary outcomes. In post-hoc testing, we compared baseline troponin concentrations between patients with and without evidence of coronary 18F-fluoride activity and also confirmed treatment efficacy by comparison of ADP-stimulated platelet activation between the two trial intervention groups (ticagrelor *versus* placebo). For 1-year evaluation of changes in cardiac troponin I concentrations, an adjusted linear regression model (adjusted for the minimisation variables) was generated and descriptive statistics were presented for the area under the curve. Where there were missing

values, the value was imputed linearly from adjacent measurements. Adjustment for age was performed as a linear term. To determine whether there was efficacy of ticagrelor using a baseline troponin I concentration ≥5 ng/L, a post-hoc comparison was made between groups using the method described in the primary analysis. For all analyses, a two-sided $p<0.05$ was taken as statistically significant. Statistical analysis was performed using SAS (Software 9.4, North Carolina) with the primary analysis validated by a second statistician in Edinburgh Clinical Trials Unit. Post-hoc analyses were performed separately from the primary statistical analysis plan using R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) by PDA.

Results

Study Population

A total of 361 patients were screened and 202 patients were randomized following the baseline coronary 18F-fluoride PET-CCTA (***Figure 1***). Eleven patients discontinued the study early due to withdrawal of consent (n=1), a new diagnosis of malignancy on baseline PET-CCTA (n=1), <80% compliance with study medication at 30 days (n=8), and a sudden unexpected death prior to receiving study medication (n=1). The randomized groups were well matched for the presence of cardiovascular risk factors and represented a high-risk cohort with 70% having a history of acute coronary syndrome (median 2.25 years prior to study enrolment) (***Table 1***). A per-protocol population of 191 patients (mean age 65.9, SD 8.3 years, 80% male) had both blood sampling at 30 days and ≥80% compliance with the study medication, comprising 94 patients in the ticagrelor group and 97 patients in the placebo group. One hundred and twenty (62.8%) patients had evidence of coronary 18F-fluoride activity in at least one epicardial vessel (***Table 2, Figure 2***).

The geometric mean troponin I concentration at baseline was 3.8 (Geometric SD 2.9) ng/L in patients with increased coronary 18F-fluoride activity compared with 2.5 (Geometric SD 2.6) ng/L in those without uptake (p=0.004; ***Table 2***) from a post-hoc analysis.

Effect of ticagrelor on platelet function

Baseline platelet and monocyte reactivities were well balanced between treatment arms. Consistent with its known pharmacological action, ticagrelor markedly inhibited platelet P-selectin expression and reduced the formation of platelet-monocyte aggregates following *ex vivo* stimulation with ADP (***Figure 3,*** p<0.001 for all). Ticagrelor had no effect on 30-day

unstimulated platelet activation (p>0.05 for all). These results were derived from post-hoc analysis.

Effect of ticagrelor on high-sensitivity troponin I at 30 days

For the primary endpoint, there was no effect of ticagrelor on troponin I at 30 days in patients who had increased coronary 18F-fluoride activity (ratio of geometric means ticagrelor *versus* placebo 1.11, 95% CI 0.90 to 1.36; p=0.32) (***Table 3***). Similarly, amongst the 71 (37.2%) patients without discernible coronary 18F-fluoride activity, there was no difference in the 30-day troponin I concentration between ticagrelor and placebo (ratio of geometric means 1.02, 95% CI 0.80 to 1.31; p=0.87) (***Table 3***).

We explored whether a reduction in cardiac troponin I could be demonstrated over twelve months. Twelve-month troponin I concentrations were measured in 183 (95.8%) patients, comprising of 91 (96.8%) patients in the ticagrelor group and 92 (94.8%) patients in the placebo group. There was no difference in area under the concentration curve of troponin I over twelve months between the ticagrelor and placebo groups (ratio of geometric means 0.92, 95% CI 0.74 to 1.13; p=0.42) (***Figure 4***) (***Table 4***). Post-hoc analysis of the subset of patients with a baseline troponin I concentration ≥5 ng/L (ticagrelor n=34, baseline geometric mean 10.3 ng/L; placebo n=33, baseline geometric mean 8.7 ng/L), found there was no change in troponin I concentration at 30 days (p=0.89) or twelve months (p=0.86). (***Supplementary Figure 1, Supplementary Table 2***).

Safety outcomes

There were no suspected unexpected serious adverse reactions over the course of this study. Serious adverse events occurred in 7/100 (7%) patients who received at least one single dose

of ticagrelor and 15/101 (11.9%) patients who were administered placebo (***Supplementary Table 3***). There were no reported major life-threatening or other major bleeding events over the course of this study. Minimal bleeding events (bruising) were reported in 64 (64.0%) patients in the ticagrelor group and 12 (11.9%) patients in the placebo group (***Supplementary Table 4***). Dyspnea episodes occurred in 24 (24%) patients in the ticagrelor group compared with 8 (7.9%) patients in the placebo group at one year.

Discussion

In this randomized placebo-controlled trial, we found no evidence that ticagrelor 90 mg twice daily reduces plasma high-sensitivity cardiac troponin I concentrations in patients with high-risk plaque and established multivessel coronary artery disease. This suggests that, in patients with high-risk coronary plaque, plasma cardiac troponin I concentrations are not attributable to subclinical myocardial injury from thrombotic microembolic injury.

Our study has several important strengths. This is the first trial to use PET-CCTA imaging with 18F-fluoride to identify patients with high-risk coronary plaque who may be at heightened risk of future coronary events and thereby have the most to gain from potent dual antiplatelet therapies. It is also the largest trial to date employing coronary plaque PET imaging. Whilst previous PET studies have used 18F-fluorodeoxyglucose to visualise inflammation within the carotid arteries as a surrogate to guide intensification of atherosclerotic therapy (12, 13), the coronary and cerebral vascular beds differ both with respect to their underlying molecular pathophysiology and also in response to the treatment effect using ticagrelor (3, 14). Second, our unique study design enabled high-risk patients with multivessel coronary disease and *in vivo* evidence of disease activity to be precisely phenotyped prior to randomization in a manner that can seldom be achieved in larger clinical outcome trials (3, 15). Finally, this is the first prospective randomized controlled trial to use high-sensitivity cardiac troponin I concentrations as a surrogate outcome measure for assessing future cardiovascular risk.

In trying to understand why $P2Y_{12}$ inhibition did not reduce cardiac troponin in this study, it is worth addressing some of the underlying assumptions in the trial design. Does coronary

18F-fluoride activity identify patients with high-risk plaque? Recent studies have found that 18F-fluoride holds potential in identifying culprit plaques in the coronary circulation by classifying patients who have a high-risk cardiovascular phenotype and culprit plaque rupture following type 1 myocardial infarction (6, 7). Histological validation indicates that 18F-fluoride preferentially binds to microcalcification in regions of plaque mineralisation, a key component of high-risk plaque (16). Hydroxyapatite, the most common form of atherosclerotic microcalcification, is extruded from apoptotic macrophages, and accumulates within necrotic cores where it may destabilise the structural integrity of the fibrous cap (17, 18). The identification of abnormal material composition of the arterial wall has clinical relevance, as these regions may lead to atherosclerotic plaque rupture manifesting as myocardial infarction, stroke or aneurysm rupture (7, 19, 20). In our cohort, the frequency of 18F-fluoride activity (>60%) in stable coronary artery disease is similar to previous estimates in patients with a high burden of coronary artery disease and prior myocardial infarction (6). This work confirms the high prevalence of coronary 18F-fluoride activity in stable patients with multivessel coronary artery disease in whom intensification of antiplatelet therapy may be considered.

A key question is whether troponin measurement below the 99th centile reflects subclinical plaque rupture with accompanying distal microvascular embolisation as has previously been posited (21). In this regard, some therapies directed at reducing the risk of atherosclerotic plaque rupture, such as pravastatin, both modify troponin concentrations and reduce the risk of myocardial infarction (22, 23). In contrast, strategies that have failed to demonstrate a reduction in cardiovascular events in the context of stable coronary artery disease, such as coronary revascularisation, attenuation of plaque inflammation and inhaled therapies for respiratory disease, have not correlated with a reduction in serial troponin concentration (24,

25, 26). If subclinical plaque thrombosis is the dominant mechanism underlying detectable troponin I concentrations in patients with stable coronary artery disease, a reduction in troponin I concentration would be expected following the administration of potent antiplatelet therapy. The lack of response to ticagrelor in this study would suggest that other contributing mechanisms to myocardial injury should be considered. The emergence of newer therapies (such as sodium/glucose cotransporter 2 inhibition) that lower blood pressure may reduce troponin concentrations through an improvement in myocardial remodelling, further raising doubts over the subclinical plaque rupture hypothesis (27, 28). In this study, high-sensitivity cardiac troponin I concentrations were higher in patients with 18F-fluoride activity, albeit the differences were small and below the established risk stratification threshold of 5 ng/L (9, 22, 29). Therefore, it seems unlikely that troponin at these concentrations reflects subclinical plaque rupture and it is perhaps unsurprising that ticagrelor treatment did not result in an early or late reduction in troponin concentration.

Previous reports have suggested that there is a high incidence of subclinical intracoronary thrombus in patients with apparently stable coronary artery disease. Indeed, some have suggested that this occurs in as many as one in seven patients (8). If this is the case, it would appear that intracoronary thrombus does not track with troponin. This suggests we require better non-invasive markers of coronary thrombosis, such as novel PET tracers (30) or non-invasive imaging (31), to use as biomarkers of cardiovascular risk and anti-thrombotic therapeutic efficacy.

There are some study limitations that we should acknowledge. This study had a modest sample size to assess the impact of ticagrelor on a readily available plasma biomarker, and a larger study would be required to assess clinical outcomes of ticagrelor use in patients with

stable coronary artery disease and coronary 18F-fluoride activity. The low baseline troponin I concentrations observed in this study may have limited power to demonstrate the benefit of ticagrelor in this population. Enrichment of the population by selecting patients with higher troponin I concentrations prior to study entry may need to be considered for future trials. It should also be acknowledged that this study was undertaken in a single centre with expertise in coronary 18F-fluoride imaging and the methods for analysing coronary 18F-fluoride activity are subject to a number of operator and scan-dependent variables. Whilst recent reports have suggested that coronary 18F-fluoride activity may hold prognostic value in stratifying high-risk populations (32), larger prospective studies evaluating the prognostic utility of coronary 18F-fluoride activity in patients with cardiovascular disease are ongoing (NCT02278211).

Conclusions

In patients with multivessel coronary artery disease and *in vivo* coronary 18F-fluoride activity, we found no evidence that intensification of antiplatelet therapy using ticagrelor 90 mg twice daily reduces plasma high-sensitivity cardiac troponin I concentration at 30 days or 1 year. These findings suggest that in this group of patients plasma high-sensitivity cardiac troponin I concentrations may not be a suitable marker to predict efficacy of $P2Y_{12}$ inhibition.

Clinical Perspectives

Competency in Medical Knowledge: High-risk coronary artery plaque and plasma high-sensitivity cardiac troponin I concentrations are associated with increased rates of cardiovascular events.

Competency in Patient Care: Patients with stable coronary artery disease and an increased risk of cardiovascular events may benefit from extended therapy with $P2Y_{12}$ inhibition.

Translational Outlook 1: Although this study used an early biomarker (30-day plasma high-sensitivity cardiac troponin I concentration) to evaluate drug efficacy, coronary 18F-fluoride activity does not appear to be useful in identifying patients who may benefit from extended $P2Y_{12}$ inhibition.

Translational Outlook 2: A detailed phenotype of coronary plaque disease activity using positron emission tomography is both feasible and practical in the setting of a randomized placebo-controlled trial.

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Relationships with industry

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References

1. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med. 2013;368(21):2004-13.

2. Fox KA, Carruthers KF, Dunbar DR, *et al*. Underestimated and under-recognized: the late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J. 2010;31(22):2755-64.

3. Wallentin L, Becker RC, Budaj A, *et al*. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045-57.

4. Bonaca MP, Bhatt DL, Cohen M, *et al*. Long-term use of Ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015;372:1791-800.

5. Gurbel PA, Bliden KP, Butler K, *et al*. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009;120(25):2577-85.

6. Dweck MR, Chow MW, Joshi NV, *et al*. Coronary arterial 18F-sodium fluoride uptake: a novel marker of plaque biology. J Am Coll Cardiol 2012;59:1539-48.

7. Joshi NV, Vesey AT, Williams MC, *et al*. 18F-fluoride positron emission tomography for identification of ruptured and high-risk coronary atherosclerotic plaques: a prospective clinical trial. The Lancet 2014;383:705-13.

8. Mann J, Davies MJ. Mechanisms of progression in native coronary artery disease: role of healed plaque disruption. Heart. 1999;82:265-8.

9. Shah AS, Anand A, Sandoval Y, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet. 2015;386:2481-8.

10. Shah AS, Griffiths M, Lee KK, *et al*. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. BMJ. 2015;350:g7873.

11. Harding SA, Din JN, Sarma J, *et al*. Flow cytometric analysis of circulating platelet-monocyte aggregates in whole blood: Methodological considerations. Thromb Haemost. 2007;98:451-6.

12. Tawakol A, Fayad ZA, Mogg R *et al*. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. J Am Coll Cardiol. 2013;62:909-17.

13. Fayad ZA, Mani V, Woodward M *et al*. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet. 2011;378:1547-59.

14. Johnston SC, Amarenco P, Albers GW, *et al*. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. N Engl J Med. 2016;375:35-43.

15. Vranckx P, Valgimigli M, Jüni P, *et al*. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicenter, open-label, randomised superiority trial. Lancet. 2018;392:940-49.

16. Irkle A, Vesey AT, Lewis DY, *et al*. Identifying active vascular microcalcification by (18)F-sodium fluoride positron emission tomography. Nat Commun. 2015;6:7495.

17. New SE, Goettsch C, Aikawa M, *et al*. Macrophage-derived matrix vesicles: an alternative novel mechanism for microcalcificaiton in atherosclerotic plaques. Circ Res. 2013;113:72-77.

18. Hutcheson JD, Goettsch C, Bertazzo S, *et al*. Genesis and growth of extracellular-vesicle-derived microcalcification in atherosclerotic plaques. Nat Mater. 2016;15:335-43.

19. Vesey AT, Jenkins WS, Irkle A, *et al*. 18F-Fluoride and 18F-fluorodeoxyglucose positron emission tomography after transient ischemic attack or minor ischemic stroke. Circ Cardiovasc Imaging. 2017;3:e004976. doi:10/1161/CIRCIMAGING.116.004976,

20. Forsythe RO, Dweck MR, McBride OMB, *et al*. 18F-Sodium fluoride uptake in abdominal aortic aneurysms: the SoFIA3 study. J Am Coll Cardiol. 2018;71:513-23.

21. Oemraswingh RM, Cheng JM, Garcia-Garcia HM, et al. High-sensitivity Troponin T in relation to coronary plaque characteristics in patients with stable coronary artery disease; results of the ATHEROREMO-IVUS study. Atherosclerosis. 2017;247:135-41.

22. Ford I, Shah ASV, Zhang R, *et al*. High-sensitivity cardiac troponin, statin therapy, and risk of coronary heart disease. J Am Coll Cardiol. 2016;25:2719-728.

23. Januzzi JL, Hahn SS, Chae CU, *et al*. Effects of tirofian plus heparin versus heparin alone on troponin I levels in patients with acute coronary syndromes. Am J Cardiol. 2000;86:713-717.

24. Welsh P, Tuckwell K, McInnes IB, Sattar N. Effect of IL-6 receptor blockade on high-sensitivity troponin T and NT-proBNP in rheumatoid arthritis. Atherosclerosis. 2016;254:167-171.

25. Everett BM, Brooks MM, Vlachos HE, *et al*. Troponin and cardiac events in stable ischemic heart disease. N Engl J Med. 2015;373:610-20.

26. Adamson PD, Anderson JA, Brook RD, *et al*. Cardiac troponin I and cardiovascular risk in patients with chronic obstructive pulmonary disease. J Am Coll Cardiol. 2018;72:1126-37.

27. Januzzi Jr JL, Butler J, Jarolim P, *et al*. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. J Am Coll Cardiol. 2019;70:704-12.

548 28. McEvoy JW, Chen Y, Rawlings A, *et al*. Diastolic blood pressure, subclinical
549 myocardial damage, and cardiac events. Implications for blood pressure control. J Am Coll
550 Cardiol. 2016;68:1713-722.
551 29. Januzzi JL Jr, Suchindran S, Coles A, *et al*. High-sensitivity Troponin I and coronary
552 computed tomography in symptomatic outpatients with suspected coronary artery disease:
553 insights from the PROMISE trial. JACC Cardiovasc Imaging. 2018; pii: S1936-
554 878X(18)30132-3.
555 30. Lohrke J, Siebeneicher H, Berger M, *et al*. 18F-GP1, a novel PET tracer designed for
556 high-sensitivity, low-background detection of thrombi. J Nucl Med. 2017;58:1094-99.
557 31. Jansen CHP, Perera D, Makowski MR, *et al*. Detection of intracoronary thrombus by
558 magnetic resonance imaging in patients with acute myocardial infarction. Circulation.
559 2011;124:416-242.
560 32. Kitagawa T, Yamamoto H, Nakamoto Y, *et al*. Predictive value of 18F-fluoride
561 positron emission tomography in detecting high-risk coronary artery disease in combined
562 with computed tomography. J Am Heart Assoc. 2018;16;7:e010224.
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Tables

Table 1.

Baseline characteristics of the study population

	Total Randomised Population (n=202)	Per Protocol population (n=191)	Ticagrelor (n=94)	Placebo (n=97)	P value (ticagrelor versus placebo)¶
Age, years	65.9±8.2	65.9±8.3	65.5±8.4	66.3±8.1	0.504
Male	162 (80)	152 (80)	74 (79)	78 (80)	0.912
Body Mass Index, kg/m^2	29.8±5.2	29.7±5.0	30.0±5.2	29.4±4.9	0.413
Medical history					
History of acute coronary syndrome	143 (71)	134 (70)	65 (69)	69 (71)	0.887
Days between ACS and randomisation*	821 (620, 1056)	821 (625, 1037)	800 (620, 970)	861 (646,1081)	
Percutaneous Coronary Intervention	163 (81)	154 (81)	75 (80)	79 (81)	0.915
Coronary Artery Bypass Grafting	40 (20)	38 (20)	18 (19)	20 (21)	0.942
Hypertension	113 (56)	105 (55)	52 (55)	53 (55)	1.000
Hypercholesterolaemia	195 (97)	185 (97)	93 (99)	92 (95)	0.228
Diabetes Mellitus	39 (19)	36 (19)	19 (20)	17 (18)	0.772
Prior Stroke/Transient Ischemic Attack	4 (2)	4 (2)	2 (2)	2 (2)	1.000

History of Atrial Fibrillation	5 (2)	5 (3)	4 (4)	1 (1)	0.346
Peripheral Vascular Disease	8 (4)	7 (4)	1 (1)	6 (6)	0.134
Medications					
Aspirin	202 (100)	191 (100)	94 (100)	97 (100)	NA
Statin	192 (95)	182 (95)	92 (98)	90 (93)	0.188
Beta-Blocker	138 (68)	130 (68)	66 (70)	64 (66)	0.637
Angiotensin Converting Enzyme Inhibitor/Angiotensin II Receptor Blocker	155 (77)	145 (76)	68 (72)	77 (79)	0.333
Hemoglobin, g/dL	14.0±1.3)	14.0±1.3	14.2±1.2	13.8±1.3	0.034
Estimated Glomerular Filtration Rate, mL/min/1.73m^2					0.547
31-60	23 (11)	22 (12)	9 (10)	13 (13)	
>60	179 (89)	169 (88)	85 (90)	84 (87)	
Total Cholesterol, mg/dL	162±39	162±39	162±39	162±35	0.852

High density lipoprotein, mg/dL	46±12	46±12	43±15	46±12	0.128
Low density lipoprotein, mg/dL	89 ±31	89±31	85±35	89±27	0.377
Triglycerides, mg/dL	159±97	151±97	159±106	151±80	0.556

Values are n (%) or mean±standard deviation
* median (interquartile range)
¶ Post-hoc analysis

Table 2.

Plasma high-sensitivity cardiac troponin I concentration (ng/L) in the per-protocol population

	Overall (n=191)	**Ticagrelor (n=94)**	**Placebo (n=97)**	**p-value¶**
Coronary 18F-Fluoride Uptake				
N	120	59	61	
Baseline	3.8±2.9	4.2±2.9	3.5±3.0	0.197
30 days	3.6±2.7	4.1±2.5	3.2±2.9	0.072
Ratio of 30 days to baseline	0.95±1.87	0.97±2.13	0.93±1.59	0.907
No Coronary 18F-Fluoride Uptake				
N	71	35	36	
Baseline	2.5±2.6	2.5±2.8	2.4±2.4	0.872
30 days	2.4±2.7	2.4±2.8	2.3±2.6	0.877
Ratio of 30 days to baseline	0.97±1.68	0.97±1.77	0.96±1.59	

Geometric mean and geometric standard deviation, back transformed from log transformed values.

¶ Post-hoc analysis

Table 3.

Plasma high-sensitivity cardiac troponin I concentration (ng/L) at 30 days for the per-protocol population

	Adjusted Geometric Mean (GSE)		**Ratio of Geometric Means**	
	Ticagrelor	**Placebo**	**(95% CI)**	**p-valve**
Cardiac troponin I, ng/L (*18F-fluoride activity*)	3.8 (1.1)	3.4 (1.1)	1.11 (0.90 to 1.36)	0.32
Cardiac Troponin I, ng/L (*No 18F-fluoride activity*)	2.4 (1.1)	2.3 (1.1)	1.02 (0.80 to 1.31)	0.87

Estimates are back transformed estimates from analysis of log transformed values at 30 days adjusting for age, sex and log transformed baseline troponin. Ratio of geometric means is Ticagrelor divided by Placebo. GSE, geometric standard error.

Table 4.

Plasma high-sensitivity cardiac troponin I concentration over 1 year for participants in per protocol population

	Adjusted Geometric Mean (GSE)		**Ratio of Geometric Means**	
	Ticagrelor	**Placebo**	**(95% CI)**	**p-valve**
AUC from 30 days to 1 year (*18F-fluoride activity*)	3.7 (1.1)	4.4 (1.1)	0.86 (0.63 to 1.17)	0.33
AUC from 30 days to 1 year (*No 18F-fluoride activity*)	2.4 (1.1)	2.3 (1.1)	1.04 (0.84 to 1.28)	0.70

Estimates are back transformed estimates from analysis of log transformed values area under curve from 30 days to 1 year adjusting for age, sex and log transformed baseline troponin. Ratio of geometric means is Ticagrelor divided by Placebo. AUC, area under curve, ng/L, GSE, geometric standard error.

Central Illustration. Using coronary 18F-fluoride to identify patients who may benefit from intensified dual antiplatelet therapy.

Coronary 18F-fluoride positron emission tomography was used to identify high-risk coronary plaque in patients with stable multivessel coronary artery disease. Randomization to intensified dual antiplatelet therapy with ticagrelor did not reduce plasma high-sensitivity cardiac troponin I concentrations at 30-days in patients with high-risk plaque.

Figure 1. Consort Diagram.

Flow diagram of the progress through the phases of the randomized trial between ticagrelor and placebo groups.

Figure 2. Intracoronary thrombus and coronary 18F-fluoride activity.

A 72-year-old female with intracoronary thrombus in the left main stem (A, B arrow). Axial reconstructions demonstrate a non-obstructive intracoronary thrombus at 11 o'clock with coronary calcification at 2 o'clock and 7 o'clock (C and D, schematic). 18F-Fluoride activity was present in the coronary plaque (E and F, schematic).

Figure 3. Flow cytometry assessment of platelet activation at baseline and 30 days.

Unstimulated (upper panels) and adenosine diphosphate (20 μmol/L) stimulated (lower panels) levels of (a) platelet activation (P-selectin expression) and (b) platelet-monocyte aggregates.

Figure 4. Plasma high-sensitivity cardiac troponin I concentration over 1 year.

Box-whisker plot of individual patient-level plasma high-sensitivity troponin I concentration (ng/L) in ticagrelor (blue) and placebo (red) groups at baseline, 1, 3, 6, 9 and 12 months. Median and interquartile range for each time point.

Ticagrelor to reduce myocardial injury in patients with high-risk coronary artery plaque

Supplementary Appendix

Supplementary Table 1.

Inclusion and Exclusion Criteria

Inclusion Criteria
For inclusion in the study subjects should fulfil the following criteria: 1. Patients aged ≥40 years with angiographically proven multivessel coronary artery disease defined as at least two major epicardial vessels with any combination of either (a) >50% luminal stenosis, or (b) previous revascularization (percutaneous coronary intervention or coronary artery bypass graft surgery). 2. Provision of informed consent prior to any study specific procedures 3. Receiving aspirin
Exclusion Criteria
Subjects should not enter the study if any of the following exclusion criteria are fulfilled: 1. An acute coronary syndrome within the last 12 months 2. An indication for dual anti-platelet therapy, such as drug eluting stent 3. Receiving thienopyridine therapy such as clopidogrel or prasugrel 4. Percutaneous coronary intervention or coronary artery bypass graft surgery within the last 3 months 5. Inability or unwilling to give informed consent 6. Women who are pregnant, breastfeeding or of child-bearing potential (women who have experienced menarche, are pre-menopausal and have not been sterilised) will not be enrolled into the trial 7. Known hypersensitivity to ticagrelor or one of its excipients 8. Active pathological bleeding or bleeding diathesis 9. Significant thrombocytopenia: platelets <100 x 10^9 /L 10. History of intracranial hemorrhage 11. Moderate to severe liver impairments (Child's Grade B or C) 12. Maintenance therapy with strong CYP3A4 inhibitors, such as ketoconazole, nefazodone, ritonavir, indinavir, atazanavir, or clarithromycin 13. Major intercurrent illness of life expectancy <1 year 14. Renal dysfunction (eGFR ≤30 mL/min/1.73m^2) 15. Contraindication to iodinated contrast agents 16. Planned coronary revascularization or major non-cardiac surgery in the next 12 months 17. Maintenance therapy with simvastatin or lovastatin at doses greater than 40mg daily 18. Receiving oral anticoagulants including warfarin, rivaroxaban, dabigatran or apixaban

Supplementary Table 2.

Post-hoc analysis of efficacy of Ticagrelor in patients with troponin I concentration ≥ *5 ng/L*

PLACEBO	Baseline 18F-fluoride uptake on PET-CT			
	Negative	Negative	Positive	Positive
	Baseline hs-cTnI <5 ng/L	Baseline hs-cTnI ≥5 ng/L	Baseline hs-cTnI <5 ng/L	Baseline hs-cTnI ≥5 ng/L
Baseline hs-cTnI, geometric mean (95% CI)	1.8 (1.4 to 2.3)	7.7 (5.9 to 10.1)	1.8 (1.4 to 2.3)	9.3 (7.2 to 12.1)
30 day hs-cTnI, geometric mean (95% CI)	1.7 (1.3 to 2.3)	7.1 (4.1 to 12.1)	1.8 (1.4 to 2.3)	8.3 (6.1 to 11.2)

TICAGRELOR	Baseline 18F-fluoride uptake on PET-CT			
	Negative	Negative	Positive	Positive
	Baseline hs-cTnI <5 ng/L	Baseline hs-cTnI >5 ng/L	Baseline hs-cTnI <5 ng/L	Baseline hs-cTnI >5 ng/L
Baseline hs-cTnI, geometric mean (95% CI)	1.8 (1.4 to 2.3)	8.7 (4.7 to 16.3)	2.3 (1.9 to 2.9)	10.3 (7.6 to 15.8)
30 day hs-cTnI, geometric mean (95% CI)	1.7 (1.3 to 2.2)	10.2 (5.2 to 20.1)	2.7 (2.1 to 3.4)	8.3 (6.1 to 11.2)

Supplementary Table 3.

Serious Adverse Events for safety population

		Ticagrelor n=100		**Placebo n=101**		**Overall n=201**	
		Number of Events	**Number of Patients**	**Number of Events**	**Number of Patients**	**Number of Events**	**Number of Patients**
Any serious adverse event		10	7 (7%)	15	12 (11.9%)	25	19 (9.5%)
Outcome	Resolved	10	7 (7%)	15	12 (11.9%)	25	19 (9.5%)
Causality	Unrelated to IMP & NIMP	9	7 (7%)	14	11 (10.9%)	23	18 (9%)
	Unrelated to IMP	1	1 (1%)	1	1 (1%)	2	2 (1%)
Expectedness	Expected	0	0 (0%)	0	0 (%)	0	0 (0%)
	Unexpected	10	7 (7%)	15	12 (11.9%)	25	19 (9.5%)
Severity	Mild	5	5 (5%)	5	4 (4%)	10	9 (4.5%)
	Moderate	5	3 (3%)	9	9 (8.9%)	14	12 (6%)
	Severe	0	0 (0%)	1	1 (1%)	1	1 (0.5%)

Supplementary Table 4.

Bleeding and Dyspnea events for safety population

		Ticagrelor n=100		**Placebo n=101**		**Overall n=201**	
		Number of Events	**Number of Patients**	**Number of Events**	**Number of Patients**	**Number of Events**	**Number of Patients**
Any bleeding event		88	64 (64%)	14	12 (11.9%)	102	76 (37.8%)
PLATO classification	Minimal	87	64 (64%)	14	12 (11.9%)	101	76 (37.8%)
	Minor	1	1 (1%)	0	0 (0%)	1	1 (0.5%)
	Major	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Major life threatening	0	0 (0%)	0	0 (0%)	0	0 (0%)
Dyspnea	At 1 year	27	24 (24%)	8	8 (7.9%)	35	32 (15.9%)

Supplementary Table 5.

Post-hoc analysis of plasma high-sensitivity cardiac troponin I concentration (ng/L) in the intention to treat population who have measurement of troponin at 30 days

	Overall (n=199)	**Ticagrelor (n=98)**	**Placebo (n=101)**
Coronary 18F-Fluoride Uptake			
N	127	62	65
Baseline	3.8±2.9	4.2±2.9	3.5±2.9
30 days	3.7±2.7	4.2±2.5	3.3±2.9
Ratio of 30 days to baseline	0.97±1.86	1.00±2.12	0.95±1.59
No Coronary 18F-Fluoride Uptake			
N	72	36	36
Baseline	2.4±2.5	2.5±2.7	2.4±2.4
30 days	2.3±2.7	2.4±2.8	2.3±2.6
Ratio of 30 days to baseline	0.96±1.68	0.96±1.77	0.96±1.59

Geometric mean and geometric standard deviation, back transformed from log transformed values.

Supplementary Table 6.

Post-hoc analysis of plasma high-sensitivity cardiac troponin I concentration (ng/L) at 30 days for the intention to treat population

	Adjusted Geometric Mean (GSE)		**Ratio of Geometric Means**	
	Ticagrelor	**Placebo**	**(95% CI)**	**p-value**
Cardiac troponin I, ng/L (*18F-fluoride activity*)	3.9 (1.1)	3.5 (1.1)	1.12 (0.92 to 1.36)	0.26
Cardiac Troponin I, ng/L (*No 18F-fluoride activity*)	2.3 (1.1)	2.3 (1.1)	1.00 (0.78 to 1.29)	0.98

Estimates are back transformed estimates from analysis of log transformed values at 30 days adjusting for age, sex and log transformed baseline troponin. Ratio of geometric means is Ticagrelor divided by Placebo. GSE, geometric standard error.

Supplementary Table 7.

Post-hoc analysis of plasma high-sensitivity cardiac troponin I concentration over 1 year for participants in intention to treat population

	Adjusted Geometric Mean (GSE)		**Ratio of Geometric Means**	
	Ticagrelor	**Placebo**	**(95% CI)**	**p-value**
AUC from 30 days to 1 year (*18F-fluoride activity*)	3.7 (1.1)	4.3 (1.1)	0.87 (0.64 to 1.17)	0.35
AUC from 30 days to 1 year (*No 18F-fluoride activity*)	2.4 (1.1)	2.3 (1.1)	1.04 (0.84 to 1.28)	0.70

Estimates are back transformed estimates from analysis of log transformed values area under curve from 30 days to 1 year adjusting for age, sex and log transformed baseline troponin. Ratio of geometric means is Ticagrelor divided by Placebo. AUC, area under curve, ng/L, GSE, geometric standard error.

Supplementary Figure 1. Plasma high-sensitivity cardiac troponin I concentration (stratified population with troponin I >5ng/L at baseline) over 1 year.

Box-whisker plot of individual patient-level plasma high-sensitivity troponin I concentration (ng/L) in ticagrelor (blue) and placebo (red) groups at baseline, 1, 3, 6, 9 and 12 months (p=ns for all values). Median and interquartile range for each time point.